Short Communication

Helicobacter Pylori Seropositivity and Colorectal Cancer Risk: A Prospective Study of Male Smokers[1]

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Abstract

Because *Helicobacter pylori* colonization can produce systemic as well as local effects, it may be associated with carcinogenesis in extra gastric target organs. The currently available data regarding a possible link between *H. pylori* seropositivity and colorectal cancer risk are limited and inconclusive. In this prospective case-control study nested within the Alpha-Tocopherol, Beta-Carotene Study cohort of Finnish male smokers aged 50–69 years, we examined the association between *H. pylori* seropositivity and incident colorectal adenocarcinoma. Separate risk estimates were derived by colorectal cancer anatomical subsite and by *H. pylori* CagA seropositivity status. Demographic, dietary, and lifestyle variables were accounted for in the data analyses using information obtained from a prerandomization questionnaire and physical examination. Baseline serum samples from 118 cases and 236 matched controls were assayed for both *H. pylori* whole cell and *H. pylori* CagA antibodies. In total, 258 (73%) and 212 (60%) subjects expressed whole cell and CagA antibodies, respectively. *H. pylori* seropositivity, defined as one or both antibody assays positive, was present in 273 (77%) subjects. None of the seropositivity results were statistically different between cases and controls. Multivariate odds ratio (95% confidence interval) estimates for whole cell, cagA, and *H. pylori* seropositivity were 1.05 (0.63–1.74), 1.17 (0.74–1.84), and 0.91 (0.53–1.55), respectively. Stratification by colorectal cancer subsite yielded similarly unremarkable results. On the basis of these data, *H. pylori* carriage does not appear to be an important risk factor for colorectal adenocarcinoma.

Introduction

According to one recent estimate, ~50% of the world's population carry *Helicobacter pylori* in their stomach (1). Yet, despite its ubiquity, the full spectrum of clinical conditions associated with this organism remains to be determined. With regard to malignant disease, *H. pylori* has been recognized as a class I human carcinogen by the International Agency for Research on Cancer (2), primarily because of extensive epidemiological data showing an association between *H. pylori* seropositivity and increased gastric cancer risk. However, it seems plausible that *H. pylori* colonization might also promote tumor formation in extra gastric target organs such as the colorectum through stimulation of circulating growth factors or other local, more site-specific mechanisms. Persistent *H. pylori* exposure induces hypergastrinemia, which is a putative trophic factor for the large bowel mucosa (3). *H. pylori* carriage can also affect the normal gastrointestinal flora as a consequence of progressive chronic gastritis with glandular atrophy and decreased acid production, which might further influence colorectal carcinogenesis.

A limited number of observational studies have previously examined the association between *H. pylori* seropositivity and colorectal cancer risk with inconsistent results (4–9). The discrepant findings reported to date may be at least partially explained by one or more of the following design features of most prior studies: clinic- or hospital-based (rather than community-based) subject populations, prevalent rather than incident colorectal cancer cases; small sample sizes; and inadequate consideration of potential confounding variables in the data analyses. The objective of this prospective, nested case-control study was to clarify and extend current knowledge regarding the relationship between *H. pylori* carriage and incident colorectal adenocarcinoma risk. Because carcinogenic mechanisms may differ by anatomical subsite within the large intestine, we derived separate risk estimates for cancers of the colon, rectum, and colorectum. In addition, overall and subsite-specific risk assessments were also conducted with respect to *H. pylori* CagA seropositivity status because *cagA*-positive *H. pylori* strains appear to induce an enhanced inflammatory response and invoke higher serum gastrin levels as compared with *cagA*-negative strains (10, 11).

Materials and Methods

Study Design. Details regarding the design and conduct of the ATBC Study[3] have been reported previously (12). In brief,

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[3] The abbreviations used are: ATBC Study, Alpha-Tocopherol, Beta-Carotene Cancer Prevention Study; ODR, absorbance ratio; OR, odds ratio; CI, confidence interval.

29,133 male smokers ages 50–69 years were recruited from communities throughout southwestern Finland between April 1985 and June 1988. Individuals with a known prior history of cancer (except nonmelanoma skin cancer) were excluded. All enrolled study participants supplied a prerandomization blood sample. Serum specimens were subsequently isolated, aliquoted, and stored deep-frozen (−70°C) for future analyses. Subjects were randomly assigned to one of four intervention groups (α-tocopherol alone, β-carotene alone, or α-tocopherol and β-carotene, or placebo) based on a complete 2×2 factorial study design. Incident cancers, including colorectal adenocarcinomas, were identified using the Finnish Cancer Registry, which provides nearly 100% case ascertainment nationwide (13). Outcomes for the present study were based on follow-up data complete through December 31, 1995 (*i.e.,* 7.5–10.75 years after start of intervention). Demographic, dietary, and lifestyle variables of interest were obtained from a baseline questionnaire and physical examination.

Cases and Controls. A total of 230 incident colorectal (ICD-9 codes 153 and 154) adenocarcinoma cases were identified in the ATBC Study cohort as of December 31, 1995. Medical records and histopathological materials were centrally reviewed for all cases. Four colon cancer cases had no histopathological specimens available and thus their diagnosis was based on medical record data only. Because of the limited volume of blood samples available from the ATBC Study participants, 118 cases with adequate sera for the planned *H. pylori* antibody measurements from previously accessed aliquots were selected. Controls were chosen from among all trial participants who were alive at the time the case was diagnosed and cancer free (except nonmelanoma skin cancer) as of December 31, 1995, with two controls matched to each case by age at randomization ($\pm$5 years), month of the baseline blood draw, study center, and intervention group assignment.

Serological Assays. *H. pylori* serum antibodies were measured by experienced laboratory technicians blinded to the status of the study subjects. Whole cell antibody (IgG immunoglobulin class) status was determined using an ELISA based on pooled, sonicated antigens derived from five *H. pylori* isolates (14). CagA antibody (IgG immunoglobulin class) status was determined using an ELISA based on a M_r 65,000 recombinant protein that was purified from *Escherichia coli* (15). Serum samples were assayed in duplicate, with the results expressed as ODRs relative to simultaneously analyzed laboratory standards. Positive results were interpreted as an ODR $\geq$ 1.0 for the whole cell antigen assay and an ODR $\geq$ 0.35 for the CagA antigen assay. For both assays, if the duplicate aliquots yielded an indeterminate result (ODR value straddled the seropositivity threshold), additional aliquots were analyzed, and the average (excluding obvious outliers) value was used to determine antibody status. Matched case and control specimens were analyzed consecutively as triplets within batches. Blinded, replicate quality control phantom samples (from known whole cell antibody seropositive and seronegative subjects) constituted ~10% (n = 40) of all specimens and were inserted near the beginning and near the end of each serum batch. On the basis of the analyses of these quality control specimens, the percentage agreement for classifying *H. pylori* seropositivity on blinded, repeated samples was 100% for the whole cell assay result alone and 98% for the whole cell assay and CagA assay results combined.

Statistical Analyses. Demographic, dietary, lifestyle, intervention, and serology variables, including age at randomization, body mass index, tobacco use, residence, education level, dietary intake (total energy, fat, fiber, folate), alcohol consumption, physical activity level, treatment assignment, and *H. pylori* antibody status (whole cell, CagA, combined), were compared between subject subgroups using either the χ^2 test, the Kruskal-Wallis test, or a Wilcoxon's rank-sum test modified to test for trend (16), as appropriate. Logistic regression models based on these predictor variables (including potentially relevant interactions between variables) were fit to estimate ORs and 95% CIs as a measure of risk for colorectal adenocarcinoma, overall and by anatomical subsite. Statistical calculations were performed using Stata computer software, version 5.0 (Stata Corporation, College Station, TX). Reported *P*s were based on two-sided tests with α equal to 0.05. Because cases and controls were matched, the mean and median values, proportions, and risk estimates presented should be interpreted as adjusted for the aforementioned matching factors.

Results

The mean follow-up time for all subjects was 7.6 (SD = $\pm$3.4) years. For case subjects, mean time to colorectal adenocarcinoma diagnosis was 3.6 ($\pm$2.2) years. As expected from the matching criteria, cases and controls had similar age and intervention group distributions. Other baseline characteristics were also comparable between cases and controls (Table 1). With respect to *H. pylori* carriage status, a total of 258 (73%) subjects was found to have whole cell antibodies, and 212 (60%) subjects were found to have CagA antibodies. By individual combinations of the two serological assay results, 197 (56%) subjects had both whole cell and CagA antibodies, 61 (17%) subjects had whole cell antibodies without CagA antibodies, 15 (4%) subjects had CagA antibodies without whole cell antibodies, and 81 (23%) subjects had neither antibody. Defined as one or both serum assays positive *versus* both assays negative, *H. pylori* seropositivity was observed among 273 (77%) subjects.

Distributions for the baseline characteristics of the subject population shown in Table 1 did not differ significantly across *H. pylori* seropositivity groups ($P > 0.05$ for each variable), with the exceptions of age ($P = 0.04$) and education level ($P < 0.01$). Whole cell, CagA, and *H. pylori* seropositivity rates were each higher among subjects who were older and among those less educated in this dataset. By case-control status, whole cell seropositivity rates were identical ($P = 1.0$) among subjects with or without colorectal adenocarcinoma (Table 2). CagA seropositivity rates were also similar between cases and controls ($P = 0.59$). On the basis of the composite serological variable, *H. pylori* seropositivity rates were 75% for cases and 78% for controls ($P = 0.59$).

Multivariate logistic regression models were fit, including a term for education level. Risk estimates for colorectal cancer based on the serum assay results were 1.05 for whole cell seropositivity, 1.17 for CagA seropositivity, and 0.91 for total *H. pylori* seropositivity (Table 2). Inclusion of cross-product terms based on the demographic, dietary, and lifestyle characteristics shown in Table 1 and *H. pylori* seropositivity status revealed no statistically significant interactions ($P > 0.05$ for each interaction variable). In addition, the cross-product term for whole cell seropositivity x CagA seropositivity was not statistically significant ($P = 0.12$). Using median age of the study sample (60 years) to define older and younger subjects, OR estimates for whole cell, CagA, and *H. pylori* seropositivity were 1.04 (0.46–2.34), 1.26 (0.61–2.58), and 0.72 (0.31–1.71) for subjects $\geq$60 years of age and 1.06 (0.55–2.05), 1.12 (0.62–2.05), and 1.06 (0.53–2.12) for subjects <60 years of age. Restric-

Table 1 Baseline characteristics of the study population by case-control status

	Controls (n = 236)	Cases (n = 118)	P^a
Age at randomization (yr)			
Mean (SD)	58.8 (4.9)	59.1 (5.3)	0.61
Median (interquartile range)	58 (55–63)	59 (55–63)	
Body mass index (kg/m^2)			
Mean (±SD)	26.5 (3.9)	26.5 (3.6)	0.74
Median (interquartile range)	26.0 (23.8–28.5)	26.1 (24.4–28.7)	
Tobacco use (pack-years)			
Mean (±SD)	36.6 (17.9)	37.2 (19.5)	0.98
Median (interquartile range)	35 (25–45)	38 (23–44)	
Residence, *n* (%)			
Rural	80 (34)	40 (34)	0.96
Urban	155 (66)	78 (66)	
Education level, *n* (%)			
Primary school or less	193 (82)	92 (78)	0.39
Junior high school or beyond	43 (18)	26 (22)	
Energy intake (kcal/day)			
Mean (±SD)	2752.7 (839.1)	2798.4 (759.0)	0.38
Median (interquartile range)	2657.6 (2128.7–3188.1)	2722.6 (2284.8–3241.2)	
Dietary fat (g/day)			
Mean (±SD)	122.4 (45.1)	122.7 (38.8)	0.49
Median (interquartile range)	115.6 (88.8–144.1)	120.5 (95.2–146.0)	
Dietary fiber (g/day)			
Mean (±SD)	24.8 (9.9)	25.8 (10.4)	0.37
Median (interquartile range)	23.3 (17.0–30.8)	25.0 (18.8–33.3)	
Dietary folate (μg/day)			
Mean (±SD)	331.6 (107.1)	331.3 (99.8)	0.98
Median (interquartile range)	317.9 (251.4–404.9)	319.3 (262.7–385.8)	
Alcohol consumption (g/day)			
Mean (±SD)	16.1 (19.6)	19.6 (21.9)	0.24
Median (interquartile range)	9.0 (1.7–24.3)	12.5 (1.9–28.1)	
Occupational physical activity, *n* (%)			
Nonworker	120 (51)	58 (49)	0.11
Sedentary	27 (11)	23 (19)	
Light	35 (15)	19 (16)	
Moderate/heavy	54 (23)	18 (15)	
Recreational physical activity, *n* (%)			
Sedentary	93 (39)	49 (42)	0.70
Active	143 (61)	69 (58)	
Intervention group, *n* (%)			
Placebo	60 (25)	30 (25)	1.00
α-Tocopherol only	70 (30)	35 (30)	
β-Carotene only	48 (20)	24 (20)	
α-Tocopherol and β-carotene	58 (25)	29 (25)	

[a] Two-sided P (α = 0.05) based on χ^2 test (categorical variables), Wilcoxon's rank-sum test modified to test for trend (ordinal variables), or Kruskal-Wallis test (continuous variables).

tion of the regression analyses to include only those colorectal cancer cases diagnosed ≥2 years from the time of randomization (n = 95) did not meaningfully alter the overall OR estimates for whole cell (OR = 1.08; 95% CI = 0.62–1.87), CagA (OR = 1.28; 95% CI = 0.78–2.11), or *H. pylori* (OR = 0.98; 95% CI = 0.55–1.74) seropositivity.

With respect to anatomical subsite, the OR estimates for colon cancer were 1.01 (0.54–1.87) for whole cell, 1.21 (0.68–2.15) for CagA, and 0.83 (0.44–1.58) for *H. pylori* seropositivity (Table 2). For rectal cancer, the OR estimates were 1.09 (0.54–2.20), 1.12 (0.60–2.08), and 1.01 (0.48–2.13), respectively. Among the subset of subjects who expressed one or both *H. pylori* antibodies, CagA-positive subjects had no significant risk elevations for colon cancer (OR = 1.85; 95% CI = 0.77–4.42), rectal cancer (OR = 1.21; 95% CI = 0.54–2.73), or colorectal cancer (OR = 1.48; 95% CI = 0.78–2.79) compared with CagA negative subjects.

Discussion

H. pylori carriage has been associated with increased risks for both gastric and extra gastric malignancies (2, 17). *H. pylori*-induced hypergastrinemia, either alone or in combination with alterations to the normal gastrointestinal flora, represents a plausible mechanism whereby colonization with this organism could promote colorectal carcinogenesis. In this nested case-control study of older Finnish male smokers, however, *H. pylori* seropositivity was not significantly associated with overall or subsite-specific risks for incident colorectal adenocarcinoma. Similarly, the presence or absence of *H. pylori* CagA antibodies did not significantly affect the observed colorectal cancer risk. On the basis of these observations, it seems doubtful that *H. pylori* carriage is an important risk factor for colorectal cancer in such populations.

A limited number of observational studies have previously examined the relationship between *H. pylori* seropositivity and

Table 2 Overall and subsite-specific associations between *Helicobacter pylori* seropositivity and colorectal adenocarcinoma

	Controls	Colon cancer cases		Rectal cancer cases		Colorectal cancer cases	
	n (%)	*n* (%)	OR (95% CI)[a]	*n* (%)	OR (95% CI)	*n* (%)	OR (95% CI)
Whole cell assay							
Negative	64 (27)	19 (29)	1.00	13 (25)	1.00	32 (27)	1.00
Positive	172 (73)	46 (71)	1.01 (0.54–1.87)	40 (75)	1.09 (0.54–2.20)	86 (73)	1.05 (0.63–1.74)
CagA assay							
Negative	97 (41)	25 (38)	1.00	20 (38)	1.00	45 (38)	1.00
Positive	139 (59)	40 (62)	1.21 (0.68–2.15)	33 (62)	1.12 (0.60–2.08)	73 (62)	1.17 (0.74–1.84)
Combined assays[b]							
Negative	52 (22)	18 (28)	1.00	11 (21)	1.00	29 (25)	1.00
Positive	184 (78)	47 (72)	0.83 (0.44–1.58)	42 (79)	1.01 (0.48–2.13)	89 (75)	0.91 (0.53–1.55)

[a] Odds ratio (95% CI) referent to controls, adjusted for education level; results should also be interpreted as adjusted for the matching factors (age at randomization, month of the baseline blood draw, study center, and intervention group assignment).
[b] Both assays negative *versus* one or both assays positive; referred to as "*H. pylori* seropositivity" within the text.

colorectal cancer risk (4–9). However, the results from these studies remain inconclusive, with two reports of a positive association (4, 9) and four reports of a null association (5–8). In the initial case-control study by Talley *et al.* (4), colorectal cancer patients were found to have a markedly higher, although nonstatistically significant, *H. pylori* seropositivity rate relative to cancer-free controls (OR = 1.72; 99% CI = 0.86–3.41). Others have speculated that an unusually low *H. pylori* seropositivity rate among the heterogeneous group of cancer-free controls (38%) may have accentuated this risk estimate (6). More recently, Fireman *et al.* (9) observed a borderline statistically significant increase in the prevalence of *H. pylori* antibodies among colorectal cancer patients relative to unmatched controls (80.4% *versus* 62.7%; $P = 0.05$). Of note, known gastritis was an exclusion criterion in this study. Yet, only 63% of cases *versus* 100% of controls underwent esophagogastroduodenoscopy, which may have magnified the difference in *H. pylori* seropositivity rates between these subject groups.

Two relatively small studies ($n = 41$ and $n = 38$ case subjects) that involved subjects recruited from among ambulatory care patient populations found no appreciable difference in *H. pylori* seropositivity rates by colorectal cancer case status (6, 7). In a hospital-based case-control study focused on the association between serum gastrin level and colorectal neoplasia risk, Penman *et al.* (5) detected similar *H. pylori* seropositivity rates between 42 patients with colorectal tumors (including 2 with benign adenomas) and an equal number of age- and gender-matched controls. In the only other prospective study reported to date (also designed to primarily address the association between serum gastrin level and colorectal cancer risk), Thorburn *et al.* (8) observed essentially identical *H. pylori* whole cell antibody seropositivity rates of 68.2 and 67.8%, respectively, among colorectal cancer cases and age-, gender-, and education-matched controls ($n = 233$ in each subject group; P not given). Although derived from a somewhat dissimilar subject population and based on a single serum marker for *H. pylori* seropositivity status, these data are consistent with the findings from our study.

Strengths of this study include the relatively large, prospectively identified subject sample, with incident cases and matched controls selected from the same target population without selection bias; classification of *H. pylori* seropositivity based on two different assay results for each subject; consideration of multiple potential confounding variables in the data analyses; and novel, independent risk assessments based on colorectal cancer anatomical subsite and *H. pylori* strain type. These overall study design features lend credence to the internal validity of our results. Furthermore, the *H. pylori* whole cell antibody seropositivity rate we observed is in keeping with previously published data from a random sample of men and women residing in southwestern Finland (18) and did not appear to be influenced by intensity of tobacco use (as defined by pack-years of smoking) in these data. Because the composition of our cohort was relatively restricted, the current findings should be extrapolated to other populations with appropriate caution, although prior investigations of some other colorectal cancer risk factors have demonstrated expected associations in this study population (19–22). Because our primary end point of interest was clinically diagnosed, incident colorectal adenocarcinoma, these data do not address the possibility that *H. pylori* may be associated with earlier phases of large bowel carcinogenesis such as premalignant neoplasia. However, other studies have examined this question (6, 7, 23, 24), and the results do not provide convincing evidence of positive association between *H. pylori* carriage and colorectal adenoma risk.

To our knowledge, this investigation includes the first reported assessment of CagA seropositivity and colorectal cancer risk. *H. pylori* strains that are *cagA* positive have been linked to a more aggressive inflammatory response, elevated serum gastrin level, and increased risk for gastric malignancies (10, 11, 15, 25). Nonetheless, CagA antibodies were only slightly more common among case subjects in this study, and the OR estimates for CagA seropositivity (overall and subsite-specific) were not statistically different from unity. Evaluation of CagA status in other studies of colorectal cancer would be useful to confirm the null association observed here.

In summary, we found no significant association between *H. pylori* seropositivity and incident colorectal adenocarcinoma in this prospective, nested case-control study. Assessments of *H. pylori* strain type and colorectal cancer subsite revealed no appreciable effect modification to the overall risk association. These findings are consistent with the majority of prior, although less comprehensive, epidemiological studies and do not support an important role for *H. pylori* carriage in colorectal carcinogenesis. Thus, additional pursuit of mechanistic hypotheses that could link *H. pylori* and colorectal cancer risk, such as measurement of serum gastrin levels among our cases and controls, did not appear warranted at this time. Additional data from investigations of benign or malignant colorectal neoplasia within cohorts having different demographic compositions from ours (*i.e.*, women, nonsmokers) may serve to strengthen these observations.

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